11:45

SIGNIFICANCE OF ISCHEMIC-APPEARING ST SEGMENT DEPRESSION DURING EXERCISE TESTING IN SYNDROME X

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Syndrome X is commonly defined as effort-provoked chest pain associated with ST segment depression (ST↓) in patients with angiographically normal coronary arteries (NCA). To assess the significance of exercise-induced ST↓ in this setting, 174 patients with effort-provoked chest pain and NCA underwent treadmill exercise testing (Bruce protocol) with 12-lead EKG monitoring. During the same week they also underwent radionuclide angiography to assess rest and exercise left ventricular ejection fraction (LVEF) and regional wall motion abnormalities (WMA). Thirty patients with ST↓ (≥ 1 mm horizontal or down-sloping ST depression on at least 2 leads) were compared to 144 patients with < 1mm or no ST shifts during exercise (NL). M=male, F=female: Data=mean±SD.

	M/F	Age	LVEF	ΔEF	WMA
ST↓	4/26	52±8	57±8%	1±8%	7/30 (23%)
NL	56/88*	49±10	52±12%	5±6%*	21/144 (15%)

ΔEF=change in LVEF from rest to exercise. *=p<.05 vs ST↓. ST↓ patients as a group had a more abnormal LVEF response to exercise, and a higher prevalence of exercise responses definitely abnormal in our laboratory for M or F (ΔEF ≤ 0 and/or WMA) (17/30, 57%) compared to NL (38/144, 26%, p<.01). However, 8 of 30 (27%) ST↓ patients had normal LV function with exercise (ΔEF>5%, no WMA). Thus, ST↓ in patients with chest pain and NCA, especially notable in women, is commonly associated with abnormal LV function during exercise, suggestive of inducible myocardial ischemia. However, approximately one-fourth of patients with chest pain and NCA who have no ST↓ also have evidence of abnormal regional and global LV function during exercise stress.

Thursday, March 7, 1991
10:30AM–12:00NOON, Room 216, East Concourse
Vignettes on Special Cardiac Metabolites

10:30

VASODILATOR DRUG TESTING IN PRIMARY PULMONARY HYPERTENSION

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No single vasodilator drug has been shown to consistently improve hemodynamics in pts with primary pulmonary hypertension (PPH). It may therefore be necessary to subject PPH pts to trials of several vasodilator drugs. Some studies have demonstrated salutary hemodynamic effects of intravenous prostaglandins and high doses of oral calcium channel blockers (CB) in PPH pts. We report the acute hemodynamic effects of the direct-acting pulmonary vasodilator prostaglandin E-1 (PGE-1) and high doses of CB in 9 pts with PPH and functional class III - IV symptoms. PGE-1 was given intravenously in incremental doses until a "significant" hemodynamic response (defined as a 33% decline in PA mean pressure or 50% drop in pulmonary vascular resistance from baseline) was obtained or adverse effects developed requiring discontinuation of drug infusion. CB was given in consecutive hourly oral doses (either Nifedipine 20 mg or Diltiazem 60 mg) until the maximum tolerated cumulative dose was reached or a significant hemodynamic response was seen.
RESULTS: A significant hemodynamic response was seen in only 1 pt following PGE-1 infusion and in no pt after CB therapy. Adverse effects necessitated discontinuation of drug challenge in all but 1 pt.
CONCLUSION: Our data indicates that a significant acute hemodynamic response to PGE-1 and CB is uncommon in PPH pts. This small potential for improvement must be considered in subjecting this group of pts to prolonged invasive drug testing.

10:45

GTP BINDING PROTEINS (G-PROTEINS) CALCIUM CHANNEL INTERACTIONS IN THE DENERVATED HEART.

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Cardiac denervation is a sequel to clinical conditions such as myocardial infarction, transplantation and diabetes. G-Proteins have been shown to directly regulate calcium (Ca^{2+}) channels. It is our hypothesis that quantitative changes in G α subunit as a result of parasympathectomy may lead to functional changes in Ca^{2+} channel activity. Sarcolemma vesicles were prepared from the left ventricle of dogs, 7 days after selective cardiac parasympathectomy. Vesicles were incubated with J-881 antiserum (gift of A. Gilman) and labelled with ^{125}-I goat anti-rabbit IgG. Density of G_o and G_s α-subunits increased by 50 and 300% respectively. Membrane vesicles fused to lipid bilayers on tip of patch clamp pipettes were used to record voltage regulated Ca^{2+} channels. 100 mM $BaCl_2$(pH-7.2) was used as charge carrier. Trans side contained 50 mM NaCl and 4 μM Bay K-8644. Both solutions were buffered with 10 mM HEPES and 5 mM TRIS (pH 7.2). In separate experiments channels could be recorded in the absence of Bay K. Channels did not exhibit spontaneous rundown over periods of up to 30 minutes. GTPγS was added to modulate the activity of endogenous G-Proteins in the vesicle preparation. Mean unitary current at 0 mV without GTPγS was 0.7 pA, with control and denervated vesicles. Unitary current in the denervated preparations increased to 2.4 pA with 100 μM GTPγS. Unitary current did not change significantly in control preparation after addition of GTPγS. Maximum response in channel open time was noted at 10 μM GTPγS, which is a 10 fold lower concentration than previously reported. We conclude that parasympathectomy increases G-Protein density in heart which may result in functional changes in Ca^{2+} channel activity as evidenced by the effects of GTPγS.

11:00

EFFECTS OF DILTIAZEM AND VERAPAMIL ON (+)PN200-110 BINDING KINETICS IN DOG CARDIAC MEMBRANES

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Effects of nondihydropyridine Ca^{2+} channel antagonists, diltiazem and verapamil, on [^{3}H] (+)PN200-110(PN), a 1,4-dihydropyridine, binding to drug receptor sites associated with Ca^{2+}channels were studied in dog cardiac membranes at 37°C. Diltiazem stimulated PN binding with the observed maximum effect at the dose of 50 μM. Diltiazem (50μM) increased maximal binding site density (Bmax) of PN binding from 62±14 to 93±12 (mean ± SEM) fmol/mg protein ($p<0.05$), but dissociation constant (K_D) did not change significantly (0.10±0.02 → 0.15±0.02nM). Thus, the increase in PN binding by diltiazem was due primarily to an increase of receptor sites density. The kinetic study revealed that both the association (4.60 → $1.36\times10^8 M^{-1}min^{-1}$, $p<0.05$) and the dissociation rate (0.066 → $0.022 min^{-1}$, $p<0.05$) of PN binding was reduced in the presence of 50 μM diltiazem, producing no significant net change of the apparent affinity. In contrast, verapamil inhibited PN binding dose-dependently. Verapamil (100 μM) increased K_D of PN binding from 0.15±0.03 to 0.37±0.05nM ($p<0.01$) without any effect on Bmax (67±10 68±12 fmol/mg protein). The kinetic study revealed that verapamil (100 μM) decreased the association rate (4.60 → $2.03\times10^8 M^{-1}min^{-1}$, $p<0.05$) and increased the dissociation rate (0.066 → $0.119 min^{-1}$, $p<0.05$) of PN binding. In conclusion, diltiazem and verapamil respectively stimulate and inhibit PN binding, suggesting actions at different site. Diltiazem appears to alter both the number of PN binding site and the PN binding characteristics.